

REMARKS

This Amendment and Remarks are filed in response to the Office Action dated November 1, 2007 wherein all pending claims are rejected.

Status of the Claims

Claims 1-83 are canceled. New claims 84-95 are added.

Support for the new claims, identified by the paragraph numbers and lines within each paragraph, is to be found in the printed published application US 2004/0151705 A1.

The new claims 84-95 are supported as follows:

Claim 84, preamble: An implantable hyaline cartilage construct, Abstract and lines 5-8 of [0078] comprising a collagenous porous support matrix, lines 4-5 of [0105] and line 1 of [0367] having pores between 100 and 300 μm , line 10 of [0153], seeded with chondrocytes activated in a tissue processor, lines 2-4 of [0136] and [0177], with a period of cyclic or constant hydrostatic pressure, lines 3-4 of [0192], between about 0.5 MPa and 5 MPa, line 7 of [0192] above atmospheric pressure, line 4 of [0192], applied at a frequency between 0.01 and 2.0 Hz, line 8 of [0192], for about 1 hour to about 30 days, line 9 and 10 of [0192], followed by a resting period of about 1 day to about 60 days, line 12-13 of [0192], under perfusion with a perfusion medium at a rate of perfusion flow between 1 μL and 500 $\mu\text{L}/\text{minute}$, line 2 of [0189], under oxygen concentration between 1% and 20%, line 6 of [0252], said activated chondrocytes synthesizing an extracellular matrix, lines 3-9 of [0124] and [0206], sulfated glycosaminoglycan (S-GAG) and DNA, lines 5-6 of [0207] wherein said activated chondrocytes synthesize at least 50% more of S-GAG and 49% more of DNA than control non-activated chondrocytes, lines 6-12 of [0228] and Table 2, Col 13.

Claim 85, chondrocytes are activated with a period of cyclic or constant hydrostatic pressure of about 3.0 MPa, is supported on line 8 of [0192] applied at a frequency of about

0.5 Hz, line 9 of {0192] for about 7 to about 14 days, line 10 of [0192] followed by a resting period of about 7 days to about 28 days, line 13 of [0192] under perfusion with a perfusion medium at a rate of perfusion flow between 5 μ L and 50 μ L/minute, line 3 of [0189] under oxygen concentration between 2% and 5%, line 6 of [0252].

Claim 86, support matrix prepared from a Type I collagen or Type II collagen, is supported on lines 5-6 of [0074] and lines 2-3 of [0151].

Claim 87, support matrix is a sponge or honeycomb-like lattice is supported on line 6 of [0149], line 2 of [0155] and line 2 of [0158].

Claim 88, the perfusion flow rate from about 5 to about 50 μ L per minute, is supported on line 3 of [0189].

Claim 89, chondrocytes are activated at an oxygen concentration of about 2%, is supported in Table 4, col. 15, and on line 1 of [0249].

Claim 90, construct implanted into a cartilage lesion, is supported on lines 1-2 of [0302] and Abstract, line 1.

Claim 91, chondrocytes are seeded in the support matrix at a cell density between about 12 and 15 millions/mL, is supported on line 10, of [0156].

Claim 92, chondrocytes activated with a cyclic or hydrostatic pressure of about 0.5 MPa, is supported on line 9 of [0223].

Claim 93, the tissue processor is a Tissue Engineering Support System (TESS™) culture unit, is supported on lines 5-7 of [0178].

Claim 94, chondrocytes are activated at the perfusion rate of about 5 µl/min, is supported in Table 3 and on line 4 of [0239].

Claim 95, 5% concentration of carbon dioxide, is supported on lines 11-12 of [0196].

Claim Rejections - 35 USC § 112

Claims 64-67, 69-71, 73-75 and 83 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Support is not found in the specification for a construct "consisting essentially of" as recited in line 1 of claim 83. The specification fails to recite "consisting essentially of".

Applicants disagree. The phrase "consisting essentially of" is a transitional phrase that limits the scope of the claims to those elements, materials or steps, specifically recited therein and to those that would not materially affect the basic and novel characteristic(s) of the claimed invention MPEP 2122.03 and *In re Herz*, 537 F.2d 549, 551-52, 190 USPQ 461, 463.

Under the MPEP 2111.03, while there is no *in haec verba* requirement, newly added claim limitations must be supported in the specification through express, **implicit**, or **inherent** disclosure.

Applicants respectfully submit that the limitations found in prior claim 83 are supported in the specification, as indicated. However, upon reconsideration and with filing of the new claims 84-95, Applicants canceled the transitional phrase and use the comprising language that is more appropriate to the instant claims.

In line 8 of claim 83, the specification fails to support or recite "repeatedly applying" a cyclic hydrostatic pressure followed by a constant atmospheric pressure".

Applicants disagree. The specification amply describes a repeated application of the cyclic hydrostatic pressure followed by the constant pressure. However, since the claim 83 is canceled and the new claim 84 does not contain this exact phrase, the rejection is moot.

In line 12 of claim 83, the specification fails to recite "extracellular matrix macromolecules Type II collagen", and support for this term is not found. While the specification discloses increased production of Type II collagen due to activation, no disclosure is found of the Type II collagen being extracellular matrix macromolecules.

Applicants disagree. However, since this term is not used in the new claim 84, the rejection is moot and should be withdrawn.

In line 12 of claim 83, the abbreviation "S-GAG" should be in parenthesis and preceded by the full name. Thereafter, only the abbreviation may be used.

Applicants disagree, however, the new claim 84 describes S-GAG by its full name sulfated glycosaminoglycan, followed by the abbreviation "S-GAG".

In lines 18-19 of claim 83, the specification fails to disclose Type II collagen and S-GAG being produced by synthesized extracellular matrix. While the specification discloses increased production of Type II collagen and S-GAG by dividing and multiplying chondrocytes, disclosure is not

found of the extracellular matrix producing Type II collagen and S-GAG.

Applicants disagree. The activation of chondrocytes results in synthesis of the extracellular matrix that is determined by increased production of S-GAG and DNA, see [124], [206] and [207].

In lines 20-22 of claim 83, the specification fails to disclose that mature chondrocytes are unable to produce extracellular matrix macromolecules. The specification discloses that mature cartilage tissue contains metabolically active non-dividing chondrocytes. Since the chondrocytes are metabolically active, the chondrocytes would appear to produce a small amount of extracellular matrix macromolecules even though not dividing.

Applicants disagree. However, these terms do not appear in the new claims 84-95.

In line 23 of claim 83, the specification fails to disclose isolating chondrocytes from human donor's joint tissue. The specification discloses only implanting the construct in a joint cartilage lesion.

Applicants disagree. For example, paragraph [127] and [130], lines 2-3 disclose a human as a typical source of obtaining chondrocytes.

In lines 25-26 of claim 83, the specification fails to support or recite "collagen containing solution, gel or thermo-reversible hydrogel" as alternatives.

Applicants disagree. Applicants disclose various embodiments of the material. Clearly, each embodiment is an alternative to another one.

In lines 28-29 and 36 of claim 83, the specification fails to support or recite "sponge, scaffold, honeycomb or lattice" as alternatives.

Applicants disagree. Support matrix section clearly discloses sponge, sponge-like structure, honeycomb-like lattice as alternatives to each other. See [149] last line

recites sponge-like structure **or** honeycomb-like lattice, and also [150], [155] and [158].

In lines 31-34 of claim 83, the specification fails to support or recite "collagen containing glycosaminoglycan, agarose or hyaluronin" and "collagen containing proteoglycan, glycoprotein, gelatin, fibronectin, laminin, bioactive peptide, growth factor or cytokine".

Applicants disagree. However, these terms are not claimed and thus the rejection is moot.

In lines 45-46 of claim 83, the specification fails to support or recite "activation regimen repeated for from about one week to about three months".

Applicants disagree. These terms are no longer claimed and the rejection is thus moot.

Applicants answered Examiner's rejections insofar as applicable to the new claims 84-95. With submission of the new claims, it is believed that all rejections are overcome and that all claims are in conditions for allowance.

Claim Rejections - 35 USC § 112

Claims 64-67, 69-71, 73-75 and 83 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In line 1 of claim 83, "consisting essentially of" is uncertain as to meaning and scope. Materials permitted and excluded by this limitation is uncertain.

Applicants disagree, however, to advance the examination, Applicants cancelled these terms from the new claims and generally responded to the Examiner on this issue above.

In line 2, and where recited in any other line of claim 83, "comprising" is confusing since line 1 recites "consisting essentially of".

Applicants disagree, however, since the new claim 84 is now drawn to "comprising", the rejection is moot.

In line 2 of claim 83, "newly developed immature" is uncertain as to meaning and scope. Being "newly" and "immature" is relative and subjective.

Applicants disagree. Any person having some understanding of English would understand that the newly means "new" and not previously in existence. Immature is an opposite to mature. Immature chondrocytes, quite obviously, in this context, would mean chondrocytes as not having the same quality as mature chondrocytes, therefore being different.

In line 5 of claim 83, reciting "95:5%" is confusing since a ratio is normally not expressed as a percent. Also, does the percent also apply to "95".

Applicants disagree. The expression means 95% of extracellular matrix and 5% of chondrocytes. These limitations are not in the new claims.

Claim 83 is confusing and unclear by being product-by-process by defining the claimed implantable construct in terms of process steps and conditions of how the construct is produced, and not setting forth clear, distinct and positive process steps in the order they are carried out such that there is a clear relationship between the steps, and each step has clear antecedent basis in a previous step. After the preamble, the claim contains only wherein clauses including process steps and conditions. Such wherein clauses do not set forth clear, distinct and positive process steps in a product-by-process claim. A product-by-process claim must set forth process steps as would be recited in a process of making the product. See MPEP 2113 and 2173.05(P) as to the proper form of a product-by-process claim.

Applicants disagree. However, the new claims are not product by process claims. The rejection is moot.

In line 2, claim 64 is unclear by not having clear antecedent basis for "said collagenous support".

Applicants disagree. The term is no longer used.

Applicants submit that they responded to all Examiner's rejections and distinguished the new claims from the previously pending claims. The new claims are in conditions for allowance.

Claim Rejections - 35 USC § 102

Claims 64-67, 69-71, 73-75 and 83 are rejected under 35 U.S.C. 102(a) as being anticipated by Smith et al (6,528,052).

Examiner argues that the prior claims 64-67, 69-71, 73-75 and 83 are anticipated by Smith et al. The (prior) claims are drawn to an implantable construct consisting essentially of a newly developed immature hyaline cartilage comprising a support matrix embedded with activated chondrocytes and an extracellular matrix produced by the activated chondrocytes wherein a ratio of extracellular matrix to chondrocytes is lower than 95:5% and wherein the chondrocytes are rejuvenated chondrocytes activated from inactive non-dividing chondrocytes to activated chondrocytes by repeatedly applying to inactive non-dividing chondrocytes embedded in the matrix a cyclic hydrostatic pressure followed by a constant atmospheric pressure wherein the activation results in cell proliferation, production of DNA, extracellular matrix macromolecules Type II collagen and S-GAG. The construct is prepared by isolating inactive chondrocytes from joint cartilage by subjecting the cartilage to enzymatic digestion, expanding the chondrocytes in a culture medium, suspending the expanded chondrocytes in a collagen solution, gel or thermo-reversible hydrogel, seeding the suspension in a support matrix which is a sponge, scaffold, honeycomb or honeycomb or lattice having pores 100 to 300 um in size. The seeded support is subjected to an activation, which comprises applying to the seeded support a cyclic hydrostatic pressure from about 0.01 to 10 MPa above atmospheric pressure at a frequency of from about 0.01 to 2 Hz for about one hour to 30 days followed by a resting period from about one day to sixty days, and the activation repeated

for about one week to about three months. During activation, perfusion with a perfusion medium is performed at a flow rate from about 1 to 50 uL per minute. The formed construct comprises more than 5% of activated chondrocytes, and has a ratio of newly synthesized extracellular matrix to activated chondrocytes in the construct lower than 95:5.

Smith et al disclose repair and regeneration of cartilage by a process that involves in vivo, ex vivo or in vitro treatment of cartilage or cartilage cells (chondrocytes) in a support such as a scaffold or collagen matrix (col 6, lines 14-16) by using a loading regiment involving conditions of intermittent application of periods of hydrostatic pressure followed by periods of recovery in situ (col 4, lines 25-31, and col 7, line 30 to col 8, line 8). The recovery period can be at atmospheric or low constant pressure (col 7, lines 48-50). In vitro treatment is performed by obtaining cartilage cells from cartilage, and applying the loading regiment conditions while culturing the cartilage cells in suspension within a scaffold/support, and implanting the resultant tissue or cells into a patient (col 9, lines 23-30, and col 11, lines 5-9). Articular chondrocytes (col 16, line 65) are isolated from cartilage using enzyme digestion (col 17, line 4). The chondrocytes can be autologous or not autologous (col 9, line 33). Articular cartilage can be regenerated and repaired (col 1, lines 41-43).

Examiner concludes that a cartilage construct produced by the process of Smith et al is the same the construct presently claimed for implantation into a cartilage lesion or defect. No difference is seen in the presently claimed process from the process of Smith et al that would result in a materially different construct. The process of Smith et al will inherently produce a construct having at least 5% activated chondrocytes, and a ratio of newly synthesized extracellular matrix to activated chondrocytes lower than 95:5.

Applicants disagree. However, in view of the new claims, Applicants submit that there is no anticipation of the new claims by Smith et al. The new claims are directed to the new hyaline cartilage prepared under a set of controlled conditions performed in and controlled by the tissue processor. These conditions are predetermined before the chondrocytes activation begins and are as stated in the claim 84 and dependent claims 85-95. Smith does not provide conditions for processing of the seeded support matrix in the tissue processor under constant perfusion flow, under oxygen or carbon dioxide atmosphere. Additionally, the instant invention, i.e., the construct fabricated under the preset set of conditions, results in substantially increased production of S-GAG and DNA by more than 50 and 49%, respectively. The yield and particularly such high yields are nowhere disclosed in Smith et al.

Anticipation requires that the anticipatory and instant inventions are the same, that is that the construct, or the method for its production are the same, as well as that the construct of the prior art and the construct of the invention function in the substantially the same way. Quite clearly that is not so. Smith does not use controlled conditions, oxygen, carbon dioxide atmosphere, perfusion rate, loading density or tissue processor that were shown to be instrumental in the functioning construct of the invention able to synthesize high amounts of proteins important for production of new cartilage implant and its incorporation into the cartilage lesion.

It is submitted that the invention is not anticipated by Smith et al and the rejections should be withdrawn. It is so respectfully requested.

Claim Rejections - 35 USC § 103

Claims 64-67,69-71,73-75 and 83 are further rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al (6,528,052) in view of Lee et al (6,306,169) and Burg

(6,991,652), and if necessary in further view of Atkinson et al (6,511,958).

The invention and Smith et al is described above.

Lee et al disclose producing an implant containing cells such as chondrocytes (col 7, line 8) by isolating the cells from tissue, proliferating the cells in a medium containing serum to obtain a sufficient number of cells, and seeding the cells in a construct (col 7, lines 13-17) such as a collagen sponge (col 12, line 17). A collagen sponge can be infiltrated with an alginate or agarose solution containing the cells, and the alginate or agarose gelled within the sponge (col 13, lines 11-25). This procedure produces a construct having mechanical function that resembles that processed by tissue to be repaired (col 4, lines 28-37).

Burg discloses forming a hydrogel-cell composition for use in forming new tissue such as cartilage. Before the cell are incorporated in a construct, the cells can be expanded in number by culturing in vitro in a medium containing serum (col 7, lines 20-29). Temperature-dependent hydrogels can be used (paragraph bridging cols 5 and 6). The hydrogels have reverse gelation properties, and are liquids at or below room temperature, and gel when warmed to higher temperatures, e.g. body temperature.

Examiner argues that when incorporating chondrocytes from cartilage into a scaffold for treatment as disclosed by Smith et al, it would have been obvious to expand the number of cells by in vitro culturing in a culture medium prior to incorporating the cells in the scaffold as suggested by Lee et al and Burg expanding the number of cells before incorporating the cells in a scaffold for implanting.

The resultant construct will be a cartilage construct as presently claimed, and will inherently have a ratio of newly synthesized extracellular matrix to activated chondrocytes of lower than 95:5. Smith et al disclose using a hydrostatic pressure and frequency of applying the pressure

that are the same or substantially the same as used in the present claims. Perfusion with a medium as claimed during treatment with hydrostatic pressure would have been obvious to provide nutrients for the cells to maintain the cells active for growth. Suspending the chondrocytes of Smith et al in a solution such as a collagen solution before seeding the cells in the matrix is suggested by Lee et al suspending cells in a solution such as collagen solution, before seeding, (col 6, line 21, and col 13, lines 11-26) that forms a second matrix component.

Examiner concludes that the collagen solution would have been expected to gel and form a scaffold for the chondrocytes. The conditions of dependent claims are suggested by conditions used by the references. Lee et al suggest a sponge and Burg suggests temperature-dependent hydrogels as a matrix for seeding cells to implant. Air contains slightly above 20% oxygen and using slightly less than 20% oxygen as in claim 70 would have been an obvious variation that would not be expected to produce a difference in result. Smith et al disclose 7.5% carbon dioxide (col 10, 17, line 10), and using 5% as in claim 71 is an obvious variation that would not be expected to produce a difference in result. Atkinson et al further disclose repairing cartilage lesions, and if needed would have further suggested conditions that can be used.

Applicants disagree. As pointed out above, Smith et al, as well as the other references do not provide the same construct as that claimed herein. Nowhere in any of the references, there is any suggestion that any of the implants disclosed by the prior art has ability and will synthesize over 50% more of S-GAG and over 49% more of DNA as does the implant construct of the instant invention, if fabricated and treated under conditions essentially consisting of the constant or cyclic hydrostatic pressure, oxygen and carbon dioxide atmosphere and under constant perfusion with a medium under certain specific rate flow, or for that matter suggest

such conditions. The above listed process conditions resulting in the unique implant construct of the present claims and its functionality are amply described in individual section outlining the importance for each of these conditions.

Examiner summarily concludes that the Smith et al and other references suggest conditions that are the same or substantially the same as in the instant claims and therefore that the suggested conditions will inherently provide results of perfusion, and oxygen and carbon dioxide concentration disclosed in the specification.

Applicants are amazed to find that when nowhere in any of the prior art references there is any mention of importance of the perfusion flow, oxygen or carbon dioxide atmosphere, these can be inherent in the prior art and/or, according to the Examiner, inherently implied from references that never described, suggested or even remotely alluded to them. There is no clairvoyance in the patent law. Either the conditions are important or not. Either they are disclosed or not. Either their use results in substantially different results from those observed and described before in the prior art or not. Specification describes importance of these conditions. The importance of variable flow is disclosed in [0186]-[0189]. Since there was no description of the perfusion flow anywhere in any of these references, such cannot be inherent or implied. The importance of reduced oxygen and presence of carbon dioxide is described in [0194]-[0196]. Since there was no description of the reduced oxygen requirement anywhere in any of these references, and the normal atmosphere does not contain reduced oxygen, such cannot be inherent or implied. Nor is there 5% carbon dioxide present in the atmosphere. Importance of the tissue processor is described in [0176]-[0185]. Its use cannot be inherent or implied. Importance of different types of hydrostatic pressure is described in [0190]-[0193]. Importance of hydrostatic pressure was disclosed by Smith but not the cyclic or constant pressure in

conjunction with other conditions. Optimization conditions for fabrication of the construct and the resulting construct and its ability to synthesize S-GAG and DNA in approximately 50% larger amounts is described in [0197]-[0209]. These are not inherent in the processing of combination of cited references. These high yields are a result of the optimization of the conditions to which the construct is subjected during its fabrication.

Applicants respectfully request Examiner to reconsider the rejections of the claims in view of the new claims and these arguments.

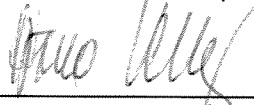
SUMMARY

In summary, previously pending claims are canceled and new claims are added. Support for the new claims is provided as well as arguments to overcome prior rejections. With this Amendment and Remarks, all claims are in conditions for immediate allowance. Notice of Allowance is respectfully solicited.

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Respectfully submitted,

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